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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/02/2003

Roland Callens

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07/01/2008

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EXAMINER

KOSAR, ANDREW D

ART UNIT

PAPER NUMBER

1654

MAIL DATE

DELIVERY MODE

07/01/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/677,215	Applicant(s) CALLENS ET AL.	
	Examiner Andrew D. Kosar	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4,6-25,27-36,39 and 40 is/are pending in the application.
- 4a) Of the above claim(s) 8,13-22,29 and 33-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-4,6,7,9-12,23-25,27,28,30-32,39 and 40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendments/Arguments

Applicant's amendments and arguments filed March 3, 2008 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below in original or modified form is herein withdrawn.

Claims 8, 13-22, 29 and 33-36 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 13, 2006.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant argues the new range limitation -30 to +60°C is not obvious because Schäfer discloses only boiling reflux conditions, Saha forms peptoids which lack chiral centers, and Mimura does not discuss elongation of the dipeptide Gly-Tyr and is carried out at 40°C. Applicant summarizes in stating that the combined teachings fail to teach/suggest the method as claimed.

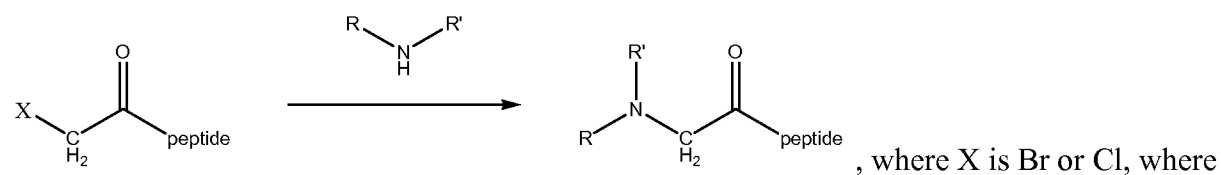
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Respectfully, the examiner disagrees. While Schäfer teaches the coupling is done at high temperatures, Mimura teaches the same fundamental coupling reaction of R-NH-R' with X-CH₂-C(O)-R'' at lower temperatures (specifically at page 3, ¶¶ [0009], [0011] and [0017] and claim 8), where the range is -20 to +30°C and -10 to +10°C. Thus, the artisan would understand from these two teachings that the range for the coupling reaction encompasses extends from -20°C to 'boiling' and would have selected any point therein to perform the reaction with the expectation that the reaction would be successful. Further, with regards to the racemization, Mimura teaches to start with the specific enantiomer one is requiring, which suggests that racemization is not induced in the reaction as disclosed. Furthermore, one cannot infer from Schäfer that the compound formed is racemic, as it is commonly accepted in the peptide arts to only denote D-amino acids with their chirality, where L is the assumed form.

Thus, one would have found motivation in the prior art to have combined the references to arrive at the instantly claimed process, particularly in modifying the temperature range in which to perform the reactions.

Claims 1-4, 6, 7, 12, 23-25, 27, 28, 30-32, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over SMALES in view of SCHÄFER (PTO-1449, 7/6/07), SAHA and MIMURA.

The instant claims are drawn to a method of making compounds via the general reaction scheme:



the product is the tetrapeptide GFLG and the amine is ammonia.

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Smales teaches the peptide GFLG (e.g. Scheme Page 1558).

The difference between Smales and the instant claims is that while Smales teaches the product, Smales does not teach the synthesis as instantly claimed.

The art recognizes reactions of various amines with haloacetylated amino acids, peptides and peptoides to generate N-Gly-peptides (e.g. Canne and Amatsu (EP 0687501A1)) and N^α-substituted Gly-peptides (e.g. Marini).

Saha teaches synthesis of peptoids, N-substituted polyglycine peptides, using bromoacetylated submonomers in the reaction (e.g. Scheme 2, page 3636). The synthesis is conducted without a resin (solution phase).

Mimura teaches synthesis of chloroacetyltyrosine (Example 1, column 4) and synthesis of GlyTyr via reaction of chloroacetyltyrosine with 28% aqueous ammonia (Example 2, column 5). Mimura teaches that the synthesis of this dipeptide via this mechanism is favored because the product can be formed in "one step in high yields." (column 3, lines 52-53).

Schäfer teaches the synthesis of trishydroxymethylmethane substituted lower peptides from the reaction of R-NH₂ with X-CH₂C(O)Y, where R is tris(hydroxymethyl)methane, X is a halogen and Y is an amino acid, di-, tri- or pentapeptide (e.g. claim 1). Schäfer further teaches the synthesis to form Tris-Gly-Gly-Arg-D-Asp-Thr from the reaction of N-2-Br-acetyl-Gly-Arg-D-Asp-Thr reacting with the tris(hydroxymethyl)methane (e.g. Example 3).

It would have been obvious to have made the peptide of Smales, or any other peptide, via reaction of the haloacetylated fragment with ammonia or any substituted amine, in order to form the final product more efficiently with fewer steps and higher yields.

One would have been motivated to have made any peptide, including the peptide GFLG,

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from the haloacetylated form in order to have an easy and quantitative route for derivitizing peptides and to reduce the number of steps in the process, such as protection/deprotection steps, increase the efficiency of the production and the yield of the product.

One would have had a reasonable expectation for success in forming the product via reaction of the haloacetylated tripeptide with ammonia, as the art recognizes that the reaction of ammonia with haloacetylated amino acids and the reaction of amines with haloacetylated peptides of any size.

Further, with regards to the temperature and concentration ranges, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. temperature ranges, concentration of reactants), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP § 2145.05). One would have been motivated to optimize the conditions in order to achieve the most efficient reaction possible, with a reasonable expectation for success, as they are art recognized variables that are routinely determined and optimized.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the

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references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-4, 6, 7, 9-12, 23-25, 27, 28, 30-32, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over SMALES in view of SCHÄFER, SAHA and MIMURA, as applied to claims 1-4, 6, 7, 9, 10, 12, 23-25, 27 28, 30-32, 39 and 40, *supra*, and in further view of ANTEUNIS (US Patent 4,725,645; PTO-1449, 10/02/03).

The instant claims are presented *supra*, and are further drawn to the method where the reactant forming products of formula (II) are activated with persilylation.

The teachings of Smales, Schäfer, Saha and Mimura are presented *supra*.

Anteunis teaches using silylated amino acids during peptide synthesis, “makes it possible to carry out a rapid coupling reaction in continuous fashion, which reaction takes place without racemisation and can be carried out in the absence of basic coreagents, with water optionally present and in the presence of known protecting agents. In addition, it enables peptides of high molecular weight to be produced in yields higher than those obtained with the known silylating agents. Moreover, the process of the invention enables the water to be chemically consumed and volatile silyl derivatives to be obtained, which facilitates the removal of the later (column 1, line 60 to column 2, line 3).

It would have been obvious to have used silyl activated peptides or amino acids to form the building blocks in order achieve rapid coupling reactions between the subunits.

One would have been motivated to silyl activate the peptides in order to increase the

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speed and efficiency of the reaction and reduce racemization of the product.

One would have had a reasonable expectation for success in forming the starting material by reaction of silyl activated peptides, as silyl activation and the subsequent use in the synthesis of peptides is a widely practiced technique that can be used to make any peptide.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 8, 13-22, 29 and 33-36 drawn to an invention nonelected with traverse in the reply filed on November 16, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Andrew D Kosar/
Primary Examiner, Art Unit 1654